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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,744	09/15/2003	John J. Quinn	1300-0008	6795

23980 7590 08/04/2006

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PALO ALTO, CA 94304-1124

EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,744	QUINN ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *28-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Specification

2. The objection to the specification is hereby withdrawn.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-27 remain rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 6,268,147 (Beattie et al.).

5. For purposes of examination, claim 1, step (b), has been construed as encompassing the simultaneous contacting of "first and second differential hybridization probes" with the amplicon, as well as the step-wise addition of said first and second differential hybridization probes, and the separate testing of different portions of the amplicon sample with said first and second differential hybridization probes.

6. Said method has been construed as encompassing the presence of different labels being present on the different (mutant and wild type) amplicons, and the probes (differential and/or capture) not being labeled, as well as the use of either or both differential hybridization and capture probe being labeled as well as the amplicon being labeled.

7. Beattie et al., teaches methods to detect of sequence variants through the stacking probes, wherein control and variant sequences are PCR amplified with labeled probes, hybridized to labeled stacking probes which are probes that are allele specific oligonucleotides (ASO) that are designed for a target variant regions, the subsequent hybridization of said labeled amplicon-ASO probe complex with an immobilized ASO on arrays or fluorescent beads designed to "capture," or hybridize to the labeled amplicon- ASO probe complex, and the detection of the labeled amplicon- ASO probe-ASO capture probe complex with arrays or flow cytometry (Figures 1, 13-15). Beattie teaches the application of said method to detect four polymorphisms that cause cystic fibrosis to immobilized ASO capture probes on arrays.

8. Beattie et al., column 8, first paragraph, discloses incorporating a label into the amplicon (target sequence).

9. Beattie et al., column 11, second paragraph, teaches the use of differential hybridization probes where the polymorphic site of interest is located either an internal or a terminal position. Beattie et al., column 20, last paragraph, teaches explicitly of using differential hybridization probes that hybridize to not only the "wild type" sequence, but also differential hybridization probes that hybridize specifically to a known mutant allele.

10. The aspect of using both a capture probe and a stacking probe (applicant's differential hybridization probe) in combination with an amplicon (target sequence) is disclosed at column 11.

11. Beattie et al., column 14, provides a non-limiting listing of suitable labels.

12. With respect to claim 1, method steps (a) and (b), and claims 6-8 and 12-14, require the isolation of nucleic acids and PCR amplification with a plurality of primers wherein one set is designed for wild type sequences, and the other set is designed for variant sequences. Beattie et al., teach "genomic DNA is first extracted from the biological sample...[the] multiplex PCR is first carried out to (using a mixture of PCR primers known to reproducibly amplify a multiplicity of specific genome fragments) to prepare the desired genomic target sequences which contain the known DNA sequence polymorphisms" (column 29, lines 19-26). ASO probes are designed for the polymorphic and control sites (column 11, lines 17-20; column 21, lines 35-37) and "single stranded PCR fragments may be generated by asymmetric PCR, by Streptavidin affinity purification when one member of a pair of PCR primers is labeled with biotin" and subsequently, "labeled oligonucleotides, annealing to the target stands immediately adjacent to each polymorphic site, are next mixed with the single-stranded amplified fragments, to introduce the label into the target stands (column 29, lines 34-36 and lines 38-42., claim limitations 12-14). Labeled moieties that can be used to identify and quantify first and second detectable signals include radioactive labels, fluorescent tags, chemiluminescent tags, enzymes that catalyze fluorescent, chemiluminescent or colored compound, biotin, and chemical groups that can be detected by mass or other spectroscopic properties (column 14, lines 11-18) (claim limitations 6-8).

13. With respect to claim 1, method step (c), Beattie et al., teach hybridization conditions in which the labeled amplicon-ASO probe are hybridized to an immobilized labeled ASO capture probe and the detection of said complex. Beattie et al., teach "hybridization is carried out at elevated temperatures or other increased stringency conditions, such at that short capture probe will not by itself form a stable duplex structure with the target sequence. Only if uninterrupted, contiguous base stacking occurs between labeled probe and surface-tethered capture probe...will a strong hybridization signal be seen" (column 8, lines 32-40). Beattie et al., teach the specific hybridization conditions of the labeled amplicon-ASO probe-ASO capture probe complex and varying temperature conditions (column 22, lines 39-58; column 24, lines 37-48).

14. With respect to claim 1, method steps (d) and (e) and claim 27, they require detection of the labeled amplicon-labeled probe-immobilized capture probe complex and determining the presence or absence of variant sequences by the relative amounts of control and variant hybridizations. Beattie et al., teach said hybridization complexes can be detected by autoradiography, microarray analysis, and fluorescence imaging that can detect fluorescence or chemiluminescence such as flow cytometry utilizing immobilized capture probes on beads (columns 26, lines 65-67, column 19, lines 24-30, column 30, lines 21-30, and column 38, lines 36-47 and Figures 1 and 15). With Beattie's method, the skilled artisan can analyze "simultaneous analysis of numerous known mutations or sequence polymorphism in single genes, a multiplicity of genes, or on a genome-wide scale" (column 19, lines 14-16*, claim limitation 27).

15. With respect to claims 2-4, 15-20, 23-25, Beattie teaches the application of said method to detect cystic fibrosis with immobilized captured probes on arrays. Beattie applies the labeled

amplicon-ASO probe-ASO capture probe method to detect cystic fibrosis. Beattie teaches "genomic DNA was isolated from peripheral blood leukocytes from normal individuals and from cystic fibrosis patients" (column 20, lines 6-8) (claim limitations 15). Beattie further teaches "to prepare natural single-stranded target DNA by PCR, primers CF163 and CF164, wherein CF164 was labeled with biotin at the 5' end, was used...to amplify a 138-bp fragment derived from exon 10 in the CFTR gene. This fragment contains four of the most frequent sites of mutations causing cystic fibrosis" (column 20, lines 6-29) (limitations of claims 16-20, 23). Beattie et al., further teaches "to prepare DNA by PCR, primer CF164 was labeled with biotin at the 5' end" (column 20, lines 1 1-20, and lines 22-23). Several target and capture probes for said mutations and its corresponding wild type sequences were designed were radioactively labeled wherein the diagnostic target and capture probes have spacer regions between them as the target and capture probes do not abut one another (column 20, lines 31-66 through column 21, lines 1-37; also illustrated in Figures 1, 13-14; limitations of claims 2-4). Beattie verifies the presence of the mutation 5F508 in cystic fibrosis patients with this method compared to those of a normal population, wherein patients are homozygous for said mutation, and the hybridization patterns for the homozygous mutation is higher than the controls, and notes "the hybridization strategy disclosed herein can be used to discriminate between homozygous and heterozygous condition at the 5F508 site" (column 23, lines 66, through column 24, line 32; limitation of claim 25).

16. With respect to claims 5, 9-11, 26, Beattie further teaches that the method of sample-labeled ASO probe-capture probe complex to detect variants can be further applied to microspheres. Beattie teaches "'bead technology' in which different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique

physical or chemical property associated with each bead" (column 38, lines 37-40; limitation claim 5). With the hybridization complex "stacking probe must be labeled with a tag that is distinguishable from the spectral property of color-coded beads" and quantitative determination of polymorphisms is done by "the quantity of label associated with each color-coded bead (quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window) will reveal the allele status at each marker or mutational site analyzed. The stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used in preannealing with a 'reference' sample and another used in preannealing with a 'test' sample, and the two samples are hybridized together with the mixture of color-coded beads, the relative binding of the two labels (from the stacking probes) to each color- coded beads will reveal the two transcriptional factors simultaneously" (column 39, lines 6-24). Beattie teaches "each polymorphic marker is represented by...a number of allele-specific probes" that are hybridized in tandem with labeled target probes and immobilized capture probes on beads and "the level of each label (from the shorter labeled probes) bound to each color-coded bead will then reveal the allelic status at each polymorphic or mutation-bearing site" and "FlowMetrix" systems are used to measure the levels of fluorescence wherein "different color codes can be distinguished using several fluorescent dyes mixed together at defined ratios at different levels, providing a large number of distinct spectral profiles" (column 40, lines 19-28; Figure 15B, limitations of claims 9-1 1 , 26). With respect to claim 21, Beattie teaches that said method can be used to detect variants including "intronic (noncoding) sequences interspersed within a gene" (column 16, line 36). With respect to claim 22, Beattie et al., teach that said method can be used for the "identification of species,

strains or individuals through the use of oligonucleotide probes and auxiliary oligonucleotides targeted to nucleotide sequences known to be unique for said species, strains or individuals" (column 19, lines 17-19). With respect to claim 24, Beattie teaches that this method is applicable to viruses, bacterial and fungi. Beattie teaches "the tandem hybridization method can also be used to unambiguously detect and identify bacterial, viral or other microbial species or strains on the basis of known, unique features of nucleic acid sequences" (column 34, lines 63-67).

Response to argument

17. At page 14 of the response received 27 April 2006, argument is presented that "Beattie et al., does [*sic*] ***not*** teach or suggest a differential hybridization probe that binds to the capture probe disclosed therein (e.g., claim 1, step b; Figure 3) and also does ***not*** teach or suggest that the stacking hybridization assay disclosed therein uses a comparison of the amounts of captured wild types and captured variant complexes to determine the presence or absence of a genetic variation." (Emphasis in the original.)

18. The above argument has been fully considered and has not been found persuasive as claim 1, step b, in contrast to applicant's representative's arguments, does not require the capture probe to bind to the stacking probe (applicant's differential hybridization probe). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

19. As for Beattie et al., not teaching comparison of signals obtained, it is noted that Beattie et al., does teach using multiple probes and that the formation of a hybridization product is detected. Clearly, if there is signal in one and none in the other, indicating wild type and not a mutant type, as taught by Beattie et al., then one has met this limitation.

20. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-27 remain rejected under 35 USC 102(b).

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

22. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS